SETTLEMENT AGREEMENT

I. PARTIES

This Settlement Agreement ("Agreement") is entered into between the United States of America, acting through the United States Department of Justice and on behalf of the Food and Drug Administration ("FDA") and its Center for Biologics Evaluation and Research ("CBER"), the National Institutes of Health ("NIH"), the Office of Acquisition Management and Policy of the Department of Health and Human Services ("HHS"), and the HHS Office of Inspector General ("OIG-HHS")(collectively the "United States"); and Steven E. Raper, M.D. ("Dr. Raper") (hereafter referred to as "the Parties"), through their authorized representatives.

II. PREAMBLE

As a preamble to this Agreement, the Parties agree to the following:

A. The settlement arises out of Dr. Raper's participation in the development of an investigational new drug to treat a certain deficiency in an enzyme called ornithine transcarbamylase (OTC). The urea cycle, located in the liver, detoxifies nitrogen and changes it to urea which is nontoxic and can then be excreted as urine. Some individuals are unable to convert nitrogen (ammonia) to urea because they are born with deficient or absent activity of OTC, an essential enzyme for making urea. A high level of ammonia is toxic to the central nervous system and as a result, hyperammonaemic coma and death may occur with OTC deficiency (OTCD).

B. A Phase I safety study of the use of a genetically engineered adenovirus being inserted into human subjects to address OTCD was reviewed by the FDA and NIH. The OTC gene was placed inside a virus called adenovirus and the virus was injected into the liver through blood vessels. The virus then carried the OTC gene into the subject's liver cells and once in the

liver cells, the OTC gene was to produce the OTC enzyme that is missing in OTCD. The studies of the safety of this drug in humans were regulated by the FDA. The research studies were funded by the NIH and by the FDA.

C. Dr. Raper is an Associate Professor of Medicine at the University of Pennsylvania. Dr. Raper was initially a sub-investigator who later became the Principal Investigator on the Investigational New Drug application in May 1999. Dr. Raper was the Principal Investigator on the FDA Orphan Products grant entitled "Adenoviral Vector-Mediated Gene Transfer for Ornithine Transcarbamylase" issued to support the OTCD study and was a sub-investigator on the OTC NIH grant.

D. The United States contends that it has certain civil claims against Dr. Raper as a result of the actions of Dr. Raper and those of his colleagues, James M. Wilson, M.D. and Steven Raper, M.D., in their studies of this new investigational drug described in paragraphs A-C above between July 1998 through September1999: false statements and claims in connection with the submission of grant applications, progress reports, and annual reports to, and receipt of federal funds from, the NIH; false statements and claims in connection with submissions to the FDA; false statements and claims in connection with the failure to obtain properly informed consent from human research participants; and false statements made to Institutional Review Boards charged with oversight of this research. In addition, the allegations contained in the FDA's Warning Letter issued to Dr. Raper on November 30, 2000 is incorporated herein by reference. The United States' contentions described above are hereinafter referred to as the "Covered Conduct."

E. Dr. Raper does not admit the contentions of the United States as set forth in Paragraph D above, and to the contrary, contends that his conduct was at all times lawful and appropriate.

F. In order to avoid the delay, uncertainty, inconvenience and expense of protracted litigation of these claims, the Parties reach a full and final settlement as set forth below.

TERMS AND CONDITIONS

NOW, THEREFORE, in consideration of the mutual promises, covenants, and obligations set forth below, and for good and valuable consideration as stated herein, the Parties agree as follows:

1. For purposes of this , the following definitions will apply:

A. "Clinical Trial" is (i) a clinical investigation (as defined by 21 CFR Section 56.102(c)) in which Dr. Raper has been identified on a Form FDA 1572 or investigator agreement for investigational medical devices as the investigator or as a subinvestigator; or (ii) an NIH-funded Clinical Trial, as defined in the NIH Grants Policy Statement (12/03) in which Dr. Raper has been identified in a pre-award or post-award action as Principal Investigator, Co-Investigator, or Other Significant Contributor as defined in C., D., and E. respectively and has a direct involvement with human research participants.

B. "Non-Trial Clinical Research" is an Institutional Review Board (IRB) approved study involving non-exempt human subjects' research (as defined by 45 CFR Part 46) in which Dr. Raper is identified to the IRB as the principal investigator or Co-investigator and has a direct involvement with human research participants.

C. "Principal Investigator" ("PI") on an NIH-funded grant or cooperative agreement grant (hereafter referred to as "grant") is that individual who is designated by the grantee as responsible for the scientific or technical aspects of the grant, including multi-project activities, and for day-to-day management of the project or program, whether referred to as the principal investigator, program director, or project leader.

D. “Co-Investigator” on an NIH-funded grant, including Multi-Project Activities, is an individual involved with the PI in the scientific development or execution of a project who devotes a specified percentage of time to the project and is considered “Key Personnel” as defined in the NIH Grants Policy Statement (rev. 12/03). An individual is not a Co-Investigator on an NIH grant the pre-award or post-award action does not identify him as providing a specified level of effort.

E. “Other Significant Contributor” is defined in the PHS 398 grant application dated September 2004 and refers to individuals who have committed in the pre-award or post-award action to contribute to the scientific development or execution of the project, but are not committing any specified measurable effort to the projects as identified in a pre-award or post-award action.

F. "Key Personnel" refers to the PI and other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Consultants also may be considered key personnel if they meet this definition. An individual is considered Key Personnel if the pre-award or post-award action identifies him as committing a specified amount greater than zero percent effort to the grant.

G. “Grant Affiliation” refers to those situations in which Dr. Raper is the PI, or Co-Investigator, or when identified as Key Personnel or Other Significant Contributor on an NIH-funded grant. Grant Affiliation does not pertain to those situations in which Dr. Raper is identified as Key Personnel or Other Significant Contributor in institutional training grants.

H. “Restricted Clinical Activity” refers to (i) Clinical Trials; (ii) Non-Trial Clinical Research in which some financial support is provided by federal funds; and (iii) any federally funded grant in which Dr. Raper has a Grant Affiliation and in which Dr. Raper participates through conducting Clinical Trials or Non-Trial Clinical Research.

I. "Multi-Project Activities" refers to an award that supports the funding of at least two related research projects that are related to a theme with collaboration and interaction among investigators to achieve a common goal.

2. Dr. Raper's name will be added to the list of restricted clinical investigators, currently entitled "Restricted List for Clinical Investigators," which is published on FDA's website. The government agrees that, once Dr. Raper fulfills all of the terms of the Agreement, the government will remove Dr. Raper's name from the Restricted List for Clinical

Investigators and place it on the "Clinical Investigators-Restrictions Removed" website list. Dr. Raper acknowledges that, once Dr. Raper fulfills all of the terms of the Agreement, information relating to this Agreement, including the fact that the restrictions have been removed, will continue to be publicly available in accordance with freedom of information laws and FDA's policies and procedures regarding public information.

3. Dr. Raper, if he so elects, will be eligible to participate without restriction in Restricted Clinical Activity on or after a date three years from the Effective Date of this Agreement by completing the educational and practical experience steps described in paragraphs 4 and 5. Dr. Raper must complete the educational step described in paragraph 4 before completing the practical experience step described in paragraph 5. Upon Dr. Raper's successful completion of these educational and practical experience steps, and the passage of not less than three years from the Effective Date of this Agreement, the parties agree that the restrictions imposed by this Agreement will be removed.

4. Dr. Raper agrees that before conducting Restricted Clinical Activity, he will complete: (a) "Introduction to the Principles and Practices of Clinical Research" (a course developed by the NIH Clinical Research Center); (b) Clinical Research Training Course (on-line training – five modules); and (c) DHHS Office for Human Research Protections (OHRP) – "Investigator 101" (available on CD Rom). Dr. Raper agrees to provide a certification to the FDA and NIH evidencing that he has successfully completed each course within 30 days of completion.

5. Dr. Raper agrees that during the period of restriction, he may conduct Restricted Clinical Activity only in a manner consistent with subparagraphs a through j, below. Moreover,

in order to become eligible to participate without restriction, as described in paragraph 3, Dr. Raper must obtain practical experience by performing Restricted Clinical Activity for at least thirty-six (36) months in a manner consistent with subparagraphs a through j, below:

a. Dr. Raper may participate in Restricted Clinical Activity one study at a time. However, Dr. Raper may submit, or be listed on, more than one grant application to the federal government for him to conduct Restricted Clinical Activity.

b. Dr. Raper will provide a copy of this Agreement to the sponsor of, and the IRB responsible for overseeing, any study in which he participates in Restricted Clinical Activity. Dr. Raper will ensure that any grant application that identifies Dr. Raper as participating in Restricted Clinical Activity submitted to the NIH by the grantee will include, in a cover letter, a description of Dr. Raper's role in the project.

c. Dr. Raper agrees that he will notify any sponsor and/or recipient of a federal grant in which Dr. Raper is to conduct a Clinical Trial involving Restricted Clinical Activity that the sponsor or grant recipient must hire an independent contract research organization (CRO) to oversee Dr. Raper's compliance with applicable regulations and this Agreement. Dr. Raper will provide a copy of this Agreement to the CRO. No reimbursement by federal funds may be sought for this expense.

d. If the study is federally funded, Dr. Raper and the grantee will ensure that the CRO complies with all of the provisions set forth in Exhibit 2.

e. If the study is federally funded, Dr. Raper and the grantee will ensure that the CRO reports to the government, on a semi-annual basis, all findings based on its review. In the event that the government does not receive such a report within 30 calendar days from the end of the 6-month period, Dr. Raper will be considered to be in breach of this Agreement, and the entire reporting period will not be credited toward the thirty-six month period described in paragraph 3.

f. Dr. Raper agrees that, while performing Restricted Clinical Activity under this paragraph, he will engage a "Medical Monitor" with expertise in human clinical research and in an area of expertise relevant to the subject of the Clinical Trial. Dr. Raper will provide a copy of this Agreement to the Medical Monitor. The Medical Monitor cannot be affiliated with the

University of Pennsylvania or Dr. Raper's employer and must be approved (i) in the case of a Clinical Trial, by FDA (if a clinical investigation as defined by paragraph 1A(i)) and/or by NIH (if an NIH-funded Clinical Trial as defined in paragraph 1A(ii); and (ii), in the case of Non-Trial Clinical Research, by NIH. Dr. Raper must obtain such approval of the Medical Monitor before entering any subject into a Clinical Trial and, if applicable, before receiving any federal funds to conduct Restricted Clinical Activity. In the event that the government determines that there is significant non-compliance with federal rules and regulations that causes the NIH and/or the FDA to have a concern for the safety of human research participants, the Medical Monitor will continue for a period of time to be determined by the Parties.

g. If the study is federally funded, Dr. Raper and the grantee will ensure that the Medical Monitor complies with all of the provisions set forth in Exhibit 1.

h. If the study is federally funded, Dr. Raper and the grantee will further ensure that the Medical Monitor reports to the government, on a semi-annual basis, all findings based on his/her review. Such reports must comply with the requirements set forth in Exhibit 1. In the event that the government does not receive such a report within thirty (30) calendar days from the end of the 6-month period, Dr. Raper will be considered to be in breach of this Agreement and the entire reporting period will not be credited toward the three year period described in paragraph 3. No reimbursement by federal funds may be sought for this expense.

i. At least thirty (30) days before Dr. Raper begins to conduct Restricted Clinical Activity work pursuant to this paragraph, Dr. Raper will submit to the government: (a) a statement of Dr. Raper's expected role in the conduct of the research; (b) a copy of the IRB-approved protocol; and (c) a copy of the written Agreements in which the Medical Monitor and/or the CRO agree to comply with all terms of this Settlement Agreement

j. Dr. Raper agrees to attend, throughout this three year period, at least two educational programs each year sponsored by or conducted by organizations with recognized expertise in the area of clinical research, on subjects relating to clinical trials (e.g., dealing with enhancing clinical trials, protection of human research participants, informed consent, and/or complying with FDA and NIH regulations). Dr. Raper agrees to provide a certification to the FDA and NIH evidencing that he has successfully completed each course within thirty days of completion.

6. Nothing in this Agreement should be construed as limiting Dr. Raper's ability to conduct research other than Restricted Clinical Activity, or to discuss such research with individuals engaged in clinical investigations and non-exempt human subjects research.

7. During the period of restriction, where Dr. Raper has a Grant Affiliation with a federally funded grant under which he does not conduct Clinical Trials or Non-Trial Clinical Research, but as part of the same grant other individuals with a Grant Affiliation are to conduct Clinical Trials or Non-Trial Clinical Research of greater than minimal risk (as defined in 45 CFR Section 46.102(i)), and the results of his non-Clinical Research could impact on the safety of the participants involved in the Clinical Research as determined by the sponsor of the IND (if a clinical investigation as defined in 21 CFR Section 56.102(c)), or otherwise by the grantee, Dr. Raper agrees to arrange for the services of a Special Monitor whose function will be to: (a) ascertain whether Dr. Raper's involvement constitutes Restricted Clinical Activity; (b) ascertain whether Dr. Raper communicates information, developed by Dr. Raper and related to the safety of human subjects to the sponsor or grantee; and (c) ascertain whether Dr. Raper complies with applicable regulatory requirements. Such Special Monitor shall report to the government on a semi-annual basis as described in Exhibit 1 as long as Dr. Raper is subject to the restrictions described in paragraph 5 of this Agreement. If Dr. Raper's involvement does constitute Restricted Clinical Activity, it shall be limited and governed by the provisions of paragraph 5 of this Agreement. Dr. Raper will provide a copy of this Agreement to the sponsor and grant recipient and such Special Monitor. No reimbursement by federal funds may be sought for the cost of the Special Monitor.

8. As used in this Agreement, the term "FDA" refers to the Director of the Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, United States Food and Drug Administration or the Director's Designee.

9. All notifications and other communications that Dr. Raper, the Medical Monitor, the CRO, or the Special Monitor is required to send the government must be addressed as follows:

9.1 To the FDA:

Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
United States Food and Drug Administration

1401 Rockville Pike Suite 200N
Rockville, MD 20852-1448

9. 2 To the NIH:

Director, Division of Grants Compliance and Oversight
Office of Policy for Extramural Research Administration
National Institutes of Health, DHHS
6705 Rockledge Drive, Suite 350
Bethesda, MD 20892-7974

10. For a three year period, Dr. Raper agrees to certify to FDA and the NIH, on an annual basis from the date of execution of this Agreement, that he is in compliance with the terms of this Agreement.

11. Dr. Raper agrees to author an article regarding lessons of human subject protections learned from the OTC trial. Dr. Raper agrees to submit an outline of such article to the United States Attorney's Office for the Eastern District of Pennsylvania (USAO). Dr. Raper agrees, in good faith, to supports the publication of a written statement authored by those

affected by this research in the same venue as his publication. Dr. Raper also agrees to volunteer to lecture about the lessons of human subject protections learned from the OTC trial in a public forum, and agrees to submit an outline of such lecture to the USAO.

12. Subject to the exceptions in Paragraph 14 below, in consideration of the obligations of Dr. Raper set forth in this Agreement, the United States (on behalf of itself, its officers, agents, agencies and departments) agrees to release Dr. Raper from any civil or administrative monetary claim the United States has or may have under the False Claims Act, 31 U.S.C. §§ 3729-3733; the Program Fraud Civil Remedies Act, 31 U.S.C. §§ 3801-3812; or the common law theories of payment by mistake, unjust enrichment, breach of contract and fraud, for the Covered Conduct.

13. In consideration of the obligations of Dr. Raper set forth in this Agreement, HHS agrees to release and refrain from instituting, directing or maintaining any disqualification, debarment, or administrative claim under 21 CFR Part 58, 45 CFR Part 76 or 48 CFR Part 9.4 against Dr. Raper for the Covered Conduct. This settlement does not constitute a civil judgment or a present civil charge pursuant to the NIH Grants Policy Statement and 45 CFR Part 76. Nothing in this Paragraph precludes HHS from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph 14, below.

14. Notwithstanding any term of this Agreement, specifically reserved and excluded from the scope and terms of this Agreement as to any entity or person are any and all of the following:

(a) Any civil, criminal or administrative claims arising under Title 26, U.S. Code (Internal Revenue Code);

(b) Any criminal liability;

(c) Except as explicitly stated in this Agreement, any administrative liability, including mandatory exclusion from Federal health care programs;

(d) Any liability to the United States (or its agencies) for any conduct other than the Covered Conduct;

(e) Any claims based upon such obligations as are created by this Agreement, including those created by Exhibit 1 attached hereto;

(f) Any claims based on a failure to deliver items or services due;

(g) Any civil or administrative claims against individuals other than Dr. Raper.

15. In the event that Dr. Raper fails to comply in good faith with any of the terms of this Settlement Agreement, or should any of Dr. Raper's representations or warrants be materially false, the United States may, at its sole discretion, exercise one or more of the following rights:

(a) seek specific performance of this Agreement and the prevailing party shall be entitled to an award of reasonable attorneys fees and costs in its favor; or

(b) exercise any other right granted by law.

16. Dr. Raper waives and will not assert any defenses he may have to any criminal prosecution or administrative action relating to the Covered Conduct, which defenses may be based in whole or in part on a contention that, under the Double Jeopardy Clause in the Fifth Amendment of the Constitution, or under the Excessive Fines Clause in the Eighth Amendment of the Constitution, this Agreement bars a remedy sought in such criminal prosecution or

administrative action. Dr. Raper agrees that this settlement is not punitive or a penalty in purpose or effect.

17. Dr. Raper fully and finally releases the United States, its agencies, employees, servants, and agents from any claims (including attorneys fees, costs, and expenses of every kind and however denominated) which he has asserted, could have asserted, or may assert in the future against the United States, its agencies, employees, servants, and agents, related to the Covered Conduct and the United States' investigation and prosecution thereof.

18. Dr. Raper agrees that all costs (as defined in 45 C.F.R. § 74.27, 45 C.F.R. Part 74 and 45 C.F.R. Part 92), where applicable, whether direct or indirect incurred by or on behalf of Dr. Raper in connection with: (a) the matters covered by this Agreement; (b) the Government's audit(s) and civil and any criminal investigation(s) of the matters covered by this Agreement; (c) Dr. Raper's investigation, defense, and corrective actions undertaken in response to the Government's audit(s) and civil and any criminal investigation(s) in connection with the matters covered by this Agreement (including attorney's fees), (d) the negotiation of this Agreement, and (e) any payment made pursuant to this Agreement, are unallowable costs under the cost principles applicable to government grants, contracts, cooperative Agreements, and other Agreements to which 45 C.F.R. Part 74 and 45 C.F.R. Part 92 applies (hereafter, "unallowable costs"). These unallowable costs will be separately estimated and accounted for by Dr. Raper and Dr. Raper will not charge such unallowable costs directly or indirectly to any grants, contracts, cooperative Agreements, or other Agreements with the United States or seek payment for such unallowable costs through any cost report, cost statement, information statement or payment request submitted by Dr. Raper or any of its departments or agencies. The parties agree

that nothing in this Agreement shall constitute a waiver of any rights the United States may have under 45 C.F.R. § 74.27, 45 C.F.R. Part 74 and 45 C.F.R. Part 92.

19. This Agreement is intended to be for the benefit of the Parties only, and by this instrument the Parties do not release any claims against any other person or entity.

20. Each party to this Agreement will bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement.

21. Dr. Raper represents that this Agreement is freely and voluntarily entered into without any degree of duress or compulsion whatsoever.

22. This Agreement is governed by the laws of the United States. The Parties agree that the exclusive jurisdiction and venue for any dispute arising between and among the Parties under this Agreement will be the United States District Court for the Eastern District of Pennsylvania.

23. This Agreement constitutes the complete Agreement between the Parties. This Agreement may not be amended except by written consent of the Parties.

24. The undersigned individuals signing this Agreement on behalf of Dr. Raper represent and warrant that they are authorized to execute this Agreement. The undersigned United States signatories represent that they are signing this Agreement in their official capacities and that they are authorized to execute this Agreement.

25. This Agreement may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same Agreement.

26. This Agreement is effective on the date of signature of the last signatory to the Agreement ("Effective Date").

27. All Parties consent to the United States' disclosure of this Agreement, and information about this Agreement, to the public.

THE UNITED STATES OF AMERICA

PATRICK L. MEEHAN
United States Attorney
Eastern District of Pennsylvania

DATED:_____ BY: _____
JAMES G. SHEEHAN
Associate United States Attorney
United States Attorney's Office
Eastern District of Pennsylvania

DATED:_____ BY: _____
DAVID R. HOFFMAN
Assistant United States Attorney
Eastern District of Pennsylvania

DATED:_____ BY: _____
LEWIS MORRIS
Chief Counsel
Office of Inspector General
United States Department of
Health and Human Services

DATED:_____ BY: _____
MARC R. WEISMAN
Director, Acquisition and
Management Policy
United States Department of
Health and Human Services

FOR STEVEN E. RAPER, M.D.

DATED:_____ BY: _____
STEVEN E. RAPER, M.D.

DATED: _____ BY: _____
MICHAEL HOLSTON, ESQ.
DRINKER, BIDDLE & REATH